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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,411	04/20/2006	Christopher S. Brook	PU60560	5432

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SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
POWERS, FIONA	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
04/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/576,411	BROOK ET AL.	
	Examiner	Art Unit	
	Fiona T. Powers	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 28-60* is/are pending in the application.

4a) Of the above claim(s) *5,6,9,15-24 and 38-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7, 8, 10-14, 28-37, 59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 to 24 and 28 to 60 are pending in the application.

Receipt is acknowledged of the preliminary amendment and information disclosure statement filed April 20, 2006, which have been entered in the file.

Information Disclosure Statement

The information disclosure statement filed April 20, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein other than the U.S. Patents have not been considered.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1 to 4, 7, 8, 10 to 14, 28 to 37, 59 and 60, drawn to compound, pharmaceutical compositions thereof, process for preparation of the compound and pharmaceutical composition and method of treating thrombocytopenia.

Group II, claim(s) 5, 6 and 15, drawn to method of enhancing platelet production.

Group II, claim(s) 9, drawn to method of agonizing the TPO receptor.

Group IV, claim(s) 16 to 18, drawn to method for enhancing the number of peripheral blood stem cells.

Group V, claim(s) 19 to 21, drawn to an in vitro or ex vivo method for enhancing stimulation of megakaryocyte maturation.

Group VI, claim(s) 22 to 24, drawn to an in vitro or ex vivo method for enhancing the survival and/or proliferation of stem cells, bone marrow cells, cord-blood cells, peripheral blood cells etc. Election of a single specific type of cell is also required.

Group VII, claim(s) 38 to 58, drawn to method of treating a degenerative disease. Election of a single specific disease e.g. multiple sclerosis, Alzheimer's disease, stroke, myocardial infarction, diabetes etc.) is also required.

The inventions listed as Groups I to VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the groups I to VII include more than one method of use and applicants are only entitled to a single method of use to be examined along with the compound.

In addition, it would be an undue burden on the examiner if all of the claims were examined in a single application as separate search considerations apply.

During a telephone conversation with Wayne Dustman on March 24, 2009 a provisional election was made without traverse to prosecute the invention of Group I, claims 1 to 4, 7, 8, 10 to 14, 28 to 37, 59 and 60. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5, 6, 9, 15 to 24 and 38 to 58 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product

claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction

requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because it is drawn to a pharmaceutical composition but the claim further recites "co-administering" which is a method step. Claim 14 is also rejected since it is dependent on claim 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the

> art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 to 4, 7, 8, 10 to 14, 28 to 37, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duffy et al. (WO 01/89457) in view of Berge et al. (Journal of Pharmaceutical Sciences, 66(1), 1-18, 1977) and Meade et al. (Biochemical Pharmacology, 41(5), 657-668, 1991) and Gimenez et al. (European Journal of Pharmacology, 344, 149-152, 1998), cited.

The claims are drawn to 2-(3,4-dimethylphenyl)-4-{[2-hydroxy-3′-(1H-tetrazol-5-yl)biphenyl-3-yl}-hydrazono)-5-methyl-2,4-dihydropyrazol-3-one choline, pharmaceutical compositions thereof, process for preparation of the compound and the pharmaceutical compositions, and method of treating thrombocytopenia using the compound.

Determination of the scope and content of the prior art (MPEP §2141.01)

Duffy et al. disclose the compound 3-{N′-[1-(3.4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazine}-2-hydroxy-3′-tetrazol-5-ylbiphenyl and pharmaceutical compositions thereof which are used in the treatment of thrombocytopenia. Note Example 12 on pages 39-40 and the Summary of the Invention on pages 3 to 5. This compound may also be called 2-(3,4-dimethylphenyl)-4-{[2-hydroxy-3′-(1H-tetrazol-5-yl)biphenyl-3-yl}-hydrazono)-5-methyl-2,4-

dihydropyrazol-3-one. Duffy et al. also disclose that pharmaceutically acceptable salts of the compounds disclosed therein may be prepared (page 4, line 26 and claim 20). A process for preparing the pharmaceutical composition is disclosed in claim 19.

Berge et al. disclose that "the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form" (page 1). Berge et al. disclose choline as an FDA approved commercially marketed salt (page 2, Table 1).

Thrombocytopenia is platelet count below the normal range. "Platelet-activating factor (PAF) is a phospholipid which, in experimental animals, has been shown, even in minute quantities, to cause a pronounced thrombocytopenia" (Meade et al., page 658 "Platelet-Activating Factor").

Gimenez et al. disclose that treatment of aged rats with cytidine 5'-diphosphocholine (CDP-choline), a precursor in platelet-activating factor (PAF) biosynthesis, decreased PAF levels by more that 65% (Gimenez et al., Abstract).

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between Duffy et al. and the instant claims is that Duffy et al. do not specifically disclose the choline salt of the compound of Example 12.

Finding of prima facie obviousness---rational and motivation (MPEP §2142-2413)

Thrombocytopenia is platelet count below the normal range. "Platelet-activating factor (PAF) is a phospholipid which, in experimental animals, has been shown, even in minute quantities, to cause a pronounced thrombocytopenia" (Meade et al., page 658 "Platelet-Activating Factor").

Gimenez et al. disclose that treatment of aged rats with cytidine 5'-diphosphocholine (CDP-choline), a precursor in platelet-activating factor (PAF) biosynthesis, decreased PAF levels by more that 65% (Gimenez et al., Abstract). Choline is used to synthesize CDP-choline. Therefore it would be expected that choline would lead to decreased levels of PAF.

One of ordinary skill in the art would have been motivated to prepare the choline salt of the compound 3-{N'-[1-(3.4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazine}-2-hydroxy-3'-tetrazol-5-ylbiphenyl disclosed by Duffy et al. with the expectation that an additional compound useful for treating thrombocytopenia would be obtained. One of ordinary skill in the art would have expected that the choline salt would have enhanced beneficial effects in the treatment of

thrombocytopenia since the choline salt would be expected to lead to a decrease in PAF and thereby treat thrombocytopenia. The claimed invention would have been rendered obvious by the teachings of the references in the absence of any unobvious or unexpected property or result.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 to 4, 7, 8, 10-14 and 28-36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 to 33 of U.S. Patent No. 7,335,649). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '649 patent claims a pharmaceutically acceptable salt of 3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazine}-2-hydroxy-3'(tetrazole-5-yl)biphenyl which would include the claimed choline salt. The '649 patent also claims pharmaceutical compositions comprising the pharmaceutically acceptable salt, process of preparing the pharmaceutical composition and method of treating thrombocytopenia using the pharmaceutically acceptable salt.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, In re Lemin, 141 USPQ 814 (C.C.P.A. 1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g. treating thrombocytopenia).

One of ordinary skill in the art would have been motivated to make the claimed compounds which are embraced by the abovementioned patents with the expectation that additional compounds useful in treating thrombocytopenia would be obtained.

Claims 1, 2 and 10 to 14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-11, 13, 15, 17 and 18 of U.S. Patent No. 7,452,874. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '874 patent generically discloses the claimed pharmaceutically acceptable salt, pharmaceutical compositions thereof, and process of preparing the pharmaceutical compositions.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, In re Lemin, 141 USPQ 814 (C.C.P.A. 1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g. treating thrombocytopenia).

One of ordinary skill in the art would have been motivated to make the claimed compounds which are embraced by the abovementioned patents with the expectation that additional compounds useful in treating thrombocytopenia would be obtained.

Claims 3, 4 and 28 to 36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 to 26 of U.S. Patent No. 7,332,481. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the '874 patent generically discloses the claimed pharmaceutically acceptable salt, pharmaceutical compositions thereof, and process of preparing the pharmaceutical compositions.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, In re Lemin, 141 USPQ 814 (C.C.P.A. 1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g. treating thrombocytopenia).

One of ordinary skill in the art would have been motivated to make the claimed compounds which are embraced by the abovementioned patents with the expectation that additional compounds useful in treating thrombocytopenia would be obtained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fiona T. Powers whose telephone number is 571-272-0702. The examiner can normally be reached on Monday - Friday 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571-272-0699. The fax phone number for the

organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fiona T. Powers/
Primary Examiner, Art Unit 1626

ftp
March 27, 2009